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FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
BOWMAN, AMY HUDSON	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,356	CZIEPLUCH ET AL.	
	Examiner	Art Unit	
	AMY BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-33,35-37,39-48, 50-54, 57, and 58* is/are pending in the application.

4a) Of the above claim(s) *32,40,42-48 and 51-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,31,33,35-37,39,41,50,54,57 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 February 2006* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 8/21/09 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 2/24/09 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 30-33, 35-37, 39-48, 50-54, 57, and 58 are pending in the application.

Applicant elected with traverse Group I, claims 30-41, 49, 50, and 54-58, as well as 'siRNA', and 'SEQ ID NO: 3', and the species 'mitotic stage', 'cancer', more specifically 'pancreatic cancer', in the reply filed on 12/31/08.

Therefore, this application contains claims 32, 40, 42-48, and 51-53, as well as the subject matter of the claims that is not directed to the elected invention, that is drawn to an invention nonelected with traverse in the reply filed on 12/31/08. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's amendments filed on 8/21/09 have been fully considered and are persuasive with regards to the rejection under 35 USC 112, 1st paragraph (written description). Therefore, this rejection has been withdrawn. However, the rejections

below are pending and upon consideration of the instant claim amendments, a new ground(s) of rejection is made as explained below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, 31, 33, 35-37, 39, 41, 50, 54, 57, and 58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for direct delivery to the SEQ ID NO: 2 mRNA transcript target of a siRNA specific for SEQ ID NO: 2, does not reasonably provide enablement for introduction of any antagonist via any means embracing broad systemic *in vivo* delivery with a resultant inhibition of SEQ ID NO: 1 and treatment of the instant breadth of cancers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The instant claims are directed to delivery of any antagonist of SEQ ID NO: 1 polypeptide via any means of delivery with a resultant inhibition of propagation of any undesired cell population or treatment of a very broad genus of cancers. With regards to the claims that specify that the agent is a siRNA, these claims also embrace broad systemic delivery with a broad effect that is not enabled.

With regards to the introduction of any antagonist via any means, the instant specification is not enabling for systemically delivering any type of antagonist. The claims are not enabled for systemically administering any agent with a predictable targeting effect. Applicant has not demonstrated that targeting SEQ ID NO: 1 (or SEQ ID NO: 2 which encodes SEQ ID NO: 1) would in fact result in inhibition of propagation of any undesired cell population or treatment of any cancer. Furthermore, the specification does not draw an adequate nexus between inhibition of expression of SEQ ID NO: 1 and the instantly recited outcomes and the claims do not even require for the disease or undesired cell population to have any actual association with the expression of SEQ ID NO: 1. With regards to cancers, for example, the specification does not draw an adequate nexus between inhibiting SEQ ID NO: 1 alone and the actual treatment of such a broad genus of cancers, wherein cancers are multifactorial diseases.

The instant claims embrace a huge genus of possible antagonists. With regards to delivery of siRNA molecules, for example, broad systemic delivery with the instantly

recited outcomes is very unpredictable. There is no guidance in the specification as filed that teaches how to deliver a siRNA via any means and mediate RNA interference *in vivo*. Although applicant has demonstrated RNA interference *in vitro*, applicant is not enabled for mediating RNA interference *in vivo* by the broadly recited methods, as delivery is known in the art to be unpredictable with regards to dsRNA duplexes.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using dsRNA. Scherer et al. (Nat. Biotechnol., 2003, 21(12), pages 1457-1465) teach that antisense oligonucleotides (ODNs), ribozymes, DNAzymes and RNA interference (RNAi) each face remarkably similar problems for effective application: efficient delivery, enhanced stability, minimization of off-target effects and identification of sensitive sites in the target RNAs. Scherer et al. teach that these challenges have been in existence from the first attempts to use antisense research tools, and need to be met before any antisense molecule can become widely accepted as a therapeutic agent.

Mahato et al. (Expert Opinion on Drug Delivery, January 2005, Vol. 2, No. 1, pages 3-28) teach that antisense oligodeoxynucleotides and double-stranded small interfering RNAs have great potential for the treatment of many severe and debilitating diseases. Mahato et al. teach that efforts have made significant progress in turning these nucleic acid drugs into therapeutics, and there is already one FDA-approved antisense drug in the clinic. Mahato et al. teach that despite the success of one product and several other ongoing clinical trials, challenges still exist in their stability, cellular uptake, disposition, site-specific delivery and therapeutic efficacy. Mahato et al. teach

that in order for siRNAs to be used as therapeutic molecules several problems have to be overcome, including: the selection of the best sequence-specific siRNA for the gene to be targeted and the ability to minimize degradation in the body fluids and tissues.

Zhang et al. (Current Pharmaceutical Biotechnology 2004, vol. 5, p.1-7) reviews the state of the art with regard to RNAi and has this to say about use in mammalian cells. "Use of siRNA in mammalian cells could be just as far-reaching, with the applications extending to functional genomics and therapeutics. But various technical issues must be addressed, especially for large-scale applications. For instance, dsRNA can be delivered to *C. elegans* by feeding or soaking, but effective delivery of siRNAs to mammalian cells will not be so simple."

As outlined above, it is well known that there is a high level of unpredictability in the RNAi art for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely a broad method of mediating RNA interference encompassing *in vivo* effects.

MPEP 2164.01
Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, **when filed**, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention.

Also, MPEP 2164.01(a)
A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, **at the time the application was filed**, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

The *in vivo* teachings of the specification are strictly prophetic. The specification demonstrates *in vitro* inhibition of hSGT with an siRNA molecule, which is enabling for direct delivery of an siRNA to the target *in vivo* with an siRNA wherein the antisense strand is complementary to instant SEQ ID NO: 2, which encodes instant SEQ ID NO: 1. This is not commensurate with delivering any antagonist of SEQ ID NO: 1 polypeptide with the desired effect of inhibiting the propagation of any undesired cell population, wherein the population isn't even required to express SEQ ID NO: 1.

The *in vitro* inhibition of hSGT via introduction of a siRNA specific for SEQ ID NO: 2 is in NBE cells (see page 20). The instant claims are directed to inhibition of propagation of any undesired cell population or treatment of any disease, more specifically any cancer, or pancreatic cancer, whereas the instant specification does not demonstrate that the broad genus of agents targeting such a broad genus of sequences would in fact treat the instant breadth of diseases. Applicant has not drawn a nexus between inhibiting the propagation of any undesired cell population or treatment of the instant diseases via inhibiting any of the instant sequences.

Given the teachings of the specification as discussed above, one skilled in the art could not predict *a priori* whether introduction of any of the instant agents via any means *in vivo* would result in successful inhibition of propagation of any undesired cell population or treatment of the instant scope of diseases. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

It is noted that the state of the art is such that one would expect to treat pancreatic carcinoma via direct inhibition of hSGT, as explained in the rejection under 35 USC 103(a), below.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, **at the time the application was filed**, would not have taught one skilled in the art how to make and/or use the **full scope** of the claimed invention without undue experimentation (see MPEP 2164.01(a)).

Response to Arguments

The amendment to the claims requiring for the polypeptide to have the amino acid sequence of SEQ ID NO: 1 overcame the portion of the rejection that was directed to the breadth of target sequences and therefore the rejection has been modified. However, the remaining elements of the rejection are pending as set forth above. Applicant has not offered arguments directed to these elements.

It is noted that applicant sets forth that the claims have been limited to siRNA molecules. However, this is not true for claim 30, for example.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 30, 31, 33, 35, 37, 39, 41, 50, and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Angeletti et al. (Cell Stress & Chaperones, 2002, 7(3), pages 258-268), Kordes et al. (Genomics, 52, 1998, pages 90-94), Jadeski et al. (Can J Physiol Pharmacol, 2002, 80(2), pages 125-135), Gansuage et al. (Cell Growth & Differentiation, Vol. 9, 1998, pages 611-617), and Bertrand et al. (Biochemical and Biophysical Research Communications, 2002, 296, pages 1000-1004).

It is noted that the instant rejection is directed to an enabled embodiment of the instant claims that of directly delivering a siRNA targeting SEQ ID NO: 2 to treat pancreatic cancer.

It is noted that the Kordes et al. reference is of record and cited on the IDS filed on 5/22/07; and the remainder of the references are of record and cited on the PTO-892 mailed on 2/24/09.

The instant claims are directed to a method of inhibiting the propagation of an undesired cell population or a method of treatment of a disease, more specifically a cancer, more specifically pancreatic cancer, via directly delivering a siRNA targeting SEQ ID NO:2, which encodes SEQ ID NO: 1 to the target human cell.

Angeletti et al. teaches that SGT/UBP is a cochaperone that negatively regulates Hsp70. Angeletti et al. teaches that SGT/UBP was shown to interact directly with Hsp70 (see abstract).

Kordes et al. teaches the isolation and characterization of human SGT.

Jadeski et al. teaches that sustained overproduction of nitric oxide (NO) can lead to cell cycle arrest and cellular apoptosis. Jadeski et al. teaches that carcinogenesis may result from mutational events following NO-mediated DNA damage and hindrance to DNA repair. In a majority of human and experimental tumors, tumor-derived NO appears to stimulate tumor progression; however, for a minority of tumors, the opposite has been reported. This apparent discrepancy may be explained by differential susceptibility of tumor cells to NO-mediated cytostasis or apoptosis, and the emergence of NO-resistant and NO-dependent clones.. Jadeski et al. teaches that NO-resistance

may be mediated by p53 inactivation, and upregulation of cyclo-oxygenase-2 and heat shock protein 70 (HSP70). Jadeski et al. teaches that selective NOS inhibitors may have a therapeutic role in certain cancers.

Gansauge et al. teaches that human pancreatic carcinoma cell lines expressed the inducible NO synthase that synthesizes NO and that endogenously produced NO induced apoptosis in all of the tested pancreatic cancer cell lines. Gansauge et al. teach that in cell cycle analysis, production of NO revealed a G1-arrest in all of the tested cell lines (see abstract).

Bertrand et al. teach that siRNAs appear to be quantitatively more efficient and its effect is lasting for a longer time in cell culture when compared to antisense oligonucleotides directed to the same target. Bertrand et al. teach that in mice, siRNA activity was observed when antisense oligonucleotide activity was not, probably due to the lower resistance of antisense oligonucleotides to nuclease degradation (see abstract). Bertrand et al. teach that the essential question of intracellular delivery is very similar for oligonucleotides and siRNAs and that many results already obtained with oligonucleotides could now be improved using siRNAs in the same conditions of delivery to cells. Bertrand et al. hypothesize that the siRNA life inside cells is longer than that of oligonucleotides (see page 1003, column 1).

It would have been obvious to directly deliver a siRNA to inhibit hSGT expression to enhance NO equilibrium to treat human pancreatic cancer.

One would have been motivated to inhibit hSGT expression to enhance NO equilibrium to treat human pancreatic cancer because Angeletti et al. teaches that

SGT/UBP is a cochaperone that negatively regulates Hsp70; Hsp70 was known to mediate NO-resistance, as evidenced by Jadeski et al.; and Gansauge et al. teaches that human pancreatic carcinoma cell lines expressed the inducible NO synthase that synthesizes NO and that endogenously produced NO induced apoptosis in all of the tested pancreatic cancer cell lines. One would have been motivated to optimize the concentration of NO in order to enhance apoptosis of pancreatic cancer cells without NO toxicity.

One would have been motivated to utilize a siRNA to inhibit hSGT because Bertrand et al. teaches the benefits of using siRNA molecules as sequence specific inhibitory molecules of target gene expression. Given the motivation in the art to inhibit hSGT in pancreatic cancer cells, as set forth above, and given that the sequence of hSGT was known, as evidenced by Kordes et al., one would have been motivated to utilize a siRNA directly delivered to the hSGT target to inhibit hSGT expression given the motivation of Bertrand et al. to use siRNA molecules as inhibitory molecules in a sequence specific fashion.

One would have had a reasonable expectation of success targeting hSGT to treat pancreatic cancer given that there was motivation to inhibit hSGT expression to alter Hsp70 activity, which in turn was known to be an element that could optimize NO, which was known to be involved in the treatment of pancreatic cancer cells, as set forth above. One would have had a reasonable expectation of success in directly delivering a siRNA to achieve this method because Bertrand et al. teaches the benefits of utilizing siRNAs in vivo to inhibit target gene expression in a sequence specific manner.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 30, 31, 33, 35-37, 39, 41, 50, 54, 57, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Angeletti et al. (Cell Stress & Chaperones, 2002, 7(3), pages 258-268), Kordes et al. (Genomics, 52, 1998, pages 90-94), Jadeski et al. (Can J Physiol Pharmacol, 2002, 80(2), pages 125-135), Gansuage et al. (Cell Growth & Differentiation, Vol. 9, 1998, pages 611-617), and Bertrand et al. (Biochemical and Biophysical Research Communications, 2002, 296, pages 1000-1004), as set forth in the rejection under 35 USC 103(a), above, further in view of Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888), Nakamura et al. (WO 2004/031237 A1), Devroe et al. (BMC Biotechnology, 2:15, 2002, pages 1-5), and Holen et al. (Nucleic Acids Research, Vol. 30, No. 8, 2002, pages 1757-1766).

It is noted that the Kordes et al. reference is of record and cited on the IDS filed on 5/22/07; and the remainder of the references are of record and cited on the PTO-892 mailed on 2/24/09.

It is noted that the instant rejection is directed to an enabled embodiment of the instant claims that of directly delivering a siRNA targeting SEQ ID NO: 2 to treat pancreatic cancer.

The instant claims are directed to a method of inhibiting the propagation of an undesired cell population or a method of treatment of a disease, more specifically a cancer, more specifically pancreatic cancer, via directly delivering a siRNA targeting SEQ ID NO:2, which encodes SEQ ID NO: 1 to the target human cell.

Elbashir et al. teach that duplexes of 21-23 nucleotide RNAs are the sequence-specific mediators of RNA interference. Elbashir et al. teach that duplexes of 21 nt siRNAs with 2 nt 3' overhangs are the most efficient triggers of sequence-specific mRNA degradation (see abstract). Elbashir et al. teach duplexes with overhangs as well as blunt ended duplexes that resulted in RNAi activity (see Figure 1, for example). Elbashir et al. teach duplexes wherein each strand is 19 nucleotides in length (see Figure 2, for example). Elbashir et al. teach that these elements provide a rational basis for the design of siRNAs in future gene targeting experiments (see abstract).

Nakamura et al. teach that the nucleotide sequence of siRNAs may be designed using a siRNA design computer program available from Ambion and teaches a protocol for selecting siRNA sequences. Nakamura et al. teach scanning the transcript beginning at the AUG codon for the presence of AA nucleotides to record potential siRNA target sites; comparing the potential target sites to the human genome database and eliminating target sequences with significant homology to other coding sequences using a BLAST search; and selecting qualifying target sequences for synthesis (see page 24).

Holen et al. teaches synthesis of several siRNAs against different sites on the same target mRNA, wherein the siRNAs demonstrated striking differences in silencing

efficiency (see abstract). Holen et al. walked siRNAs in three nucleotide increments to determine the effect on silencing efficiency (see Figure 2), thus demonstrating that siRNA activity is routinely optimized by shifting target position across the mRNA sequence. The siRNAs resulted in varying activity, although each did result in silencing.

Devroe et al. teach that retroviruses are efficient vectors for delivery of siRNA into mammalian cells (see Abstract/Conclusions).

It would have been obvious to design a siRNA for a method of inhibiting hSGT, as explained above, wherein the siRNA comprises a sequence as defined by SEQ ID NO: 3 and is delivered in a retroviral vector.

It would have been prima facie obvious to perform routine optimization to walk the known hSGT target sequence to design any given siRNA against the sequence in view of the guidelines taught by Elbashir et al. and Nakamura et al., as noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular element used was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. It was known in the art that the activity of a siRNA duplex can be optimized by shifting the target sequence, as evidenced by Holen et al.

Since the target sequence was known and it was known and there was motivation in the art to inhibit hSGT to treat pancreatic cancer via directly delivering a siRNA, as set forth in the rejection under 35 USC 103(a) above, one would have been motivated to apply the design guidelines of Elbashir et al. and Nakamura et al., as each teach that siRNAs are sequence specific inhibitory molecules and teach specific guidelines and recommendations for designing optimal siRNAs directed to a given sequence. Furthermore, Elbashir et al. sets forth a rational basis for the design of siRNAs.

One would have been motivated to deliver the siRNA with a retroviral vector because Devroe et al. teaches that such vectors are efficient for siRNA delivery and are an improvement over previously available methods.

With regards specifically to the siRNA comprising a sequence defined by SEQ ID NO: 3 and of any size, siRNAs of this genus are within the genus that would result from routine optimization of the guidelines/testing set forth by Elbashir et al., Nakamura et al., and Holen et al. Applicant has not demonstrated any unexpected result for a siRNA of any length comprising SEQ ID NO: 3, wherein sequences within this genus would have resulted from the rational design of siRNAs to hSGT following the published guidance of Elbashir et al., Nakamura et al. and Holen et al.

In view of the availability of targeting guidelines, as taught by Elbashir et al. and Nakamura et al., and the known optimization of siRNA duplexes via walking the target sequence, as evidenced by Holen et al., one of skill would have been able to envision every siRNA directed to the instant target hSGT sequence. Although the relative

activities would need to be experimentally determined, the majority of such siRNAs designed via the rules established in the art have some level of RNA interference activity.

As set forth in MPEP 2144.08, a species is obvious in view of the genus where one of skill would be able to immediately envision each species. Although the instant genus is large, one of skill would have been able to immediately envision each species of siRNA molecules targeted to RAD1 in view of the guidelines discussed above. It would have been obvious to one of skill to select any given siRNA targeted to hSGT based on the guidelines of Elbashir et al. and Nakamura et al. and the optimization of Holen et al. via shifting frame to yield optimal siRNAs.

Finally, one of skill in the art would have had a reasonable expectation of success at generating a siRNA duplex comprising SEQ ID NO: 3 because the tools and guidelines for siRNA design were readily available to the skilled artisan at the time of filing. Therefore, one would expect for the guidelines established in the art to result in the instantly recited molecules. Furthermore, Elbashir et al. teaches rational design guidelines for siRNA molecules including length requirements.

One would have had a reasonable expectation of success in utilizing a retroviral vector to deliver the hSGT siRNA directly to pancreatic cancer cells given that Devroe et al. teaches that such vectors are efficient for siRNA delivery and are an improvement over previously available methods.

Although the genus of possible siRNA molecules that would be produced by the guidelines of the prior art is very large, it is within the realm of routine optimization to

determine optimal siRNA molecules from the genus. The genus of siRNA molecules directed to the instant target sequence is described in the art because the target sequence was known and guidelines were established for designing siRNAs to a given target. Therefore, one of skill in the art had the tools to aid and predict which siRNA molecules will have the required function, and can readily make and test the siRNAs for resultant RNAi activity, consistent with the published Written Description Guidelines (i.e. Example 12).

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant argues that the cited references teach away from the invention because the art sets forth that HSP70 increases NO-resistance of cells and therefore one would try to increase SGT to minimize the expression of HSP70.

However, the art does not teach away from inhibiting SGT because the art sets forth motivation to alter the levels of HSP70 to optimize NO.

One would have been motivated to inhibit hSGT expression to enhance NO equilibrium to treat human pancreatic cancer because Angeletti et al. teaches that SGT/UBP is a cochaperone that negatively regulates Hsp70; Hsp70 was known to mediate NO-resistance, as evidenced by Jadeski et al.; and Gansauge et al. teaches that human pancreatic carcinoma cell lines expressed the inducible NO synthase that

synthesizes NO and that endogenously produced NO induced apoptosis in all of the tested pancreatic cancer cell lines.

Therefore, one would have been motivated to optimize the concentration of NO in order to enhance apoptosis of pancreatic cancer cells without NO toxicity.

It is noted that claim 36 is directed to the siRNA being defined by SEQ ID NO:3 and/or SEQ ID NO: 4. It is not clear what the metes and bounds of "defined by" are and therefore the claim is not in fact closed to these specific sequences. Should applicant close the claim(s) to direct delivery of the specific siRNA consisting of SEQ ID NOs: 3 and 4, these specific sequences are not considered obvious.

New Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 50 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As amended, claim 50 recites "A method of treating a comprising administering..." and is therefore incomplete. The metes and bounds of the claim cannot be determined. Appropriate correction is required.

For purposes of the instant search and corresponding examination, the claim is interpreted as being directed to treating a cancer, given this is consistent with the remainder of the claims.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tracy Vivlemore can be reached on (571) 272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMY BOWMAN
Primary Examiner
Art Unit 1635

/AMY BOWMAN/
Primary Examiner, Art Unit 1635